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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,311	07/18/2001	Roberto A Macina	DEX-0184	8561

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/16/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,311	MACINA, ROBERTO A	
	Examin r	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *7-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11,12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1 and 6, in Paper No. 14 is acknowledged. The traversal is on the ground(s) that "the special technical feature linking the claims is not an antibody to SEQ ID NO:2 it is the discovery that SEQ ID NO:2 is a cancer marker and with respect to claims 1-7, the restriction requirement contradicts the search and written opinion from this examiner in the PCT application" (see pages 6-7 of response). This argument is found to be partially persuasive. The special technical feature linking the claims in not that SEQ ID NO:2 is associated with cancer because claim 7 is directed only to an antibody to CC2 which is taught in the WO 96/39541 reference and claims 1-5 do not recite SEQ ID NO:2. In addition the restriction requirement does not contradict the search and written opinion because the WO 96/39541 was cited in the search and written opinion. Upon further consideration the examiner will rejoin Group II with Group I. With regard to Groups III-V, these groups are patentably distinct and as stated above do not have a special technical feature. With regards to the search burden, clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 7-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 15.

3. Claims 1-6 are under examination.

Specification

4. The disclosure is objected to because of the following informalities:

a. The first line of the specification needs to be updated to indicate all US applications to which priority is being claimed.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-6 are indefinite for reciting "measuring the levels of CC2 in cells, tissues, or bodily fluids in a patient" in claims 1-5 because the exact meaning of the phrase is not clear. Is the levels measured in the cells, tissue, or bodily fluid from gastrointestinal samples or as in claim 1, stomach or small intestine or other sources?. Are the level measured in human samples or other animals? In addition is the normal sample from any source or from a normal source that is the same as the cancerous source only normal tissue?

b. Claims 1 and 6 are indefinite for reciting "wherein a change in measured levels of CC2" because the exact meaning of the phrase is not clear. Is the level increased or decreased in the cancerous vs. normal sample?

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims recite measuring the level of CC2. The specification only discloses CC2 as a nucleic acid sequence as SEQ ID NO:1 which encodes the polypeptide of SEQ ID NO:2. There is no other structure or structural features disclosed in the specification for any other CC2 molecule or what structures are needed to be a CC2 molecule which is broadly encompassed by the term "CC2". Thus, the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to detecting, diagnosing, staging, monitoring, diagnosing metastasis by determining the level of SEQ ID NO:1 or 2 in a cell and comparing the level to a normal control for detecting cancer of the small intestine, stomach, and colon. SEQ ID NO:1 is a nucleic acid and SEQ ID NO:2 is the protein encoded by SEQ ID NO:1. The claims broadly encompass determining the level with a nucleic acid or antibody probe.

The specification discloses the expression at the mRNA level of SEQ ID NO:1 in stomach, small intestine, colon, bladder, kidney, liver, lung, mammary gland, pancrease, prostate, testis, uterus, endometrium (see Table 2). The specification discloses that CC2 is differentially expressed in stomach, small intestine, and colon cancer samples (see page 22). The specification also discloses, however, that in the

twenty-three matching samples for colon cancer 17 showed upregulation for the mRNA in the cancer samples but 6 samples showed lower expression in the cancer samples compared to normal adjacent tissue. In addition, in the two small intestine samples one had higher levels of expression in the cancer tissue and one had higher levels in the normal tissues. In the stomach tissue a similar pattern is disclosed. In the 20 samples, 15 tissues are found to have higher levels in the cancer tissues vs. normal and 5 normal tissues have higher expression than the cancer tissues (see Table 2).

The specification does not enable any method of detecting, staging, diagnosing, monitoring, diagnosing metastasis of any gastrointestinal cancer of the colon, stomach, or small intestine by determining the CC2 in a cell by detection of SEQ ID NO:2 with an antibody or detecting SEQ ID NO:1. The specification does not teach that there is a differential level of expression of the protein or that the protein is expressed at all in the cancerous tissues or that there are differences in the expression (of the mRNA or the protein) at different stages or that one can determine metastasis by determining the expression or level of SEQ ID NO:1 or SEQ ID NO:2.

Those of skill in the art recognize that expression of mRNA, specific for a tissue type, does not necessarily correlate nor predict equivalent levels of polypeptide expression. In fact, evidence abounds in which protein levels do not correlate with steady-state mRNA levels or alterations in mRNA levels. For example, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA levels in blast cells taken from patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. Further,

Powell et al (Pharmacogenesis, 1998, Vol. 8, pp. 411-421, abstract) teach that mRNA levels for cytochrome P450 E1 did not correlate with the level of corresponding protein, and conclude that the regulation of said protein is highly complex. Vallejo et al (Biochimie, 2000, vol. 82, pp. 1129-1133, abstract) teach that no correlation was found between NRF-2 mRNA and protein levels suggesting post-transcriptional regulation of NRF-2 protein levels. These references serve to demonstrate that the analysis of levels of polynucleotide transcripts cannot be relied upon to anticipate levels of protein expression. Further, Jang et al (Clinical and Experimental Metastasis, 1997, vol. 15, pp. 469-483, abstract) teach that further studies are necessary to determine if changes in protein levels track with changes in mRNA levels for metastasis associated genes in murine tumor cells, thus providing further evidence that one of skill in the art cannot anticipate that the level of a specific mRNA expressed by a cell will be paralleled at the protein level due to complex homeostatic factors controlling translation and post-translational modification. In addition Pennica et al (PNAS 95:14717-22, 1998) teach that the copy number is amplified but the RNA expression is actually reduced. Thus, the predictability of protein translation and its possible utility as a diagnostic are not necessarily contingent on the levels of mRNA expression due to the multitude of homeostatic factors affecting transcription and translation. Therefore, absent evidence of the protein's expression including the correlation to a diseased state, one of skill in the art would be unable to predictably use the polypeptides in any diagnostic setting without undue experimentation.

The claims are broadly drawn to detection, diagnosing, staging, monitoring, diagnosing metastasis of colon, small intestine and stomach cancer in a patient by determining the level of SEQ ID NO:1.

The diagnostic methods include for example hybridization techniques, polymerase chain reaction, as well as reverse transcription polymerase chain reaction.

The specification asserts that SEQ ID NO:1 was differentially expressed in colon, stomach, and small intestine cancerous tissue. However, the obtained results set forth in the specification in Table 2 are not indicative of diagnosing or detection of cancer because of the inconsistencies of finding in some normal matched tissues have higher levels of expression of SEQ ID NO:1 vs. cancerous tissues. In addition the specification does not teach that there are changes in the level of SEQ ID NO:1 or CC2 for staging, monitoring, or metastasis. The specification does not enable one of ordinary skill in the art to definitively assess the incidence of cancer or staging, or metastasis in a test sample.

Applicants have not set forth any supporting evidence that suggests that SEQ ID NO:1 or SEQ ID NO:2 are unique tumor or molecular markers for gastrointestinal cancer, specifically, small intestine, colon, or stomach cancers. The molecular-based techniques presented in the specification do not take into account the possibility that results from such diagnostic tests can be obscured by the presence of excess normal DNA. Tascilar et al. (Annals of Oncology 10,Suppl. 4:S107-S110, 1999) reports on diagnostic methods in the realm of pancreatic tissue, however this review article is relevant to Applicants' claimed invention. It is art known that molecular-based assays

are valid tools used in predicting and detecting diseases, however as assessed in the Tascilar review "...these tests should be interpreted with caution...". and "the genetic changes found in sources other than the pancreas itself (blood, stool) should be evaluated prudently".

Furthermore, Tockman et al. (Cancer Research 52:2711s-2718s, 1992) teach considerations necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract. Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. "This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation

against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section. Tockman reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder is highly speculative and unpredictable.

Based on the analysis and the teachings presented above it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention. Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims and to practice the invention as claimed.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00

am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER